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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,849	06/27/2002	William Hugold Velander	AIB-08252	2472

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,849	VELANDER, WILLIAM HUGOLD	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,42,56-58 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,42,56-58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 6, 2010 has been entered.

Claims 1-39, 41, 43-55, 59, 60 are cancelled. Claims 40, 42, 61 are amended.

Claims 40, 42, 56-58, 61, drawn to a drawn to a composition comprising milk derived from a transgenic mammal and a recombinant human prothrombin, wherein the Gla domain of prothrombin is gamma-carboxylated, are under consideration.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, Seegers et al., 1950, Blood, 5: 421-433, previously cited, van Cott and Velander,

1998, Expert Opinion on Investigational Drugs, 7: 1683-1690, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009, September 1, 2009, February 19, 2010, July 7, 2010.

Claims 40, 42, 56, and 58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734 previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009, September 1, 2009, February 19, 2010, July 7, 2010. It is noted that the rejection of claims 44, 46 are withdrawn as the claims are cancelled.

Claims 40 and 57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al., US Patent 4,873,316, patented October 10, 1989, in view of Jorgensen et al., 1987, The Journal of Biological Chemistry, 262: 6729-6734, previously cited, in view of Seegers et al., 1950, Blood 5: 421-433, previously cited, Le Bonniec et al., 1991, The Journal of Biochemistry, 266: 13796-13803, previously cited, Velander et al., 1992, PNAS, USA, 89: 12003-12007, see IDS, for reasons of record, February 4, 2009, September 1, 2009, February 19, 2010, July 7, 2010.

With regard to the claims being amended to the milk comprising recombinant prothrombin at a concentration of at least 1.5mg/ml, at the time of filing, the art teaches that transgenic animals can express a range of concentrations of recombinant protein in milk. Meade et al. teach that mice produced 0.2-0.5 ug/ml of TPA in milk (Meade et al.,

col. 7, 3rd parag.) and Velander et al. teach that pigs produced hPC in milk as high as 1000 ug/ml/hour (Velander et al., page 12003, 1st col., 2nd parag.). Given that transgenic animals can produce recombinant protein at a range of concentrations in milk, it would have been routine for an artisan to arrive at an animal that expresses prothrombin at 1.5 mg/ml in milk.

Applicant's arguments filed October 6, 2010 have been fully considered but they are not persuasive.

Applicant indicates that claim 40 is amended to clarify that the "milk composition derived from a transgenic mammal" comprises "human prothrombin protein" and that the prothrombin concentration is "at least 1.5 mg/ml." Applicant indicates that a milk composition derived from a transgenic mammal comprising at least 1.5 mg/ml of a human prothrombin is not found in the prior art. Applicant indicates that the courts have generally considered the biotechnological arts as "unpredictable," where in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (Applicant's emphasis, Applicant's response, pages 4-5). In response, this is not persuasive. With regard to Applicant indicating that none of the cited prior art teaches 1.5 mg/ml of human prothrombin in milk, as indicated above, an artisan would have arrived at a mammal that produced 1.5 mg/ml of human prothrombin in milk because the art teaches that there are transgenic mammals that produce low and high concentrations of recombinant protein in milk. While an artisan cannot predict which transgenic mammals will produce 1.5 mg/ml of human prothrombin, it is not beyond an

artisan's ability to make transgenic mammals and arrive at one that expresses recombinant proteins at 1.5 mg/ml. The instant specification teaches making expression constructs (specification, Example 1) and that mice and pigs comprising these constructs can be made (specification, Example 3). Because the method steps taught in the specification are the same as those taught by Meade et al. and Velander et al., an artisan would have reasonable expectation of success in arriving at transgenic mammals that produce human prothrombin in milk at concentrations of at least 1.5 mg/ml. With regard to Applicant referring to unpredictable factors such as chemical reactions and physiological activity in In re Fisher, this is not persuasive because making transgenic mammals that express recombinant proteins in milk is routine. While an artisan realizes that not all transgenic mammal generated will express recombinant protein at 1.5 mg/ml, an artisan will recognize that a transgenic mammal that expresses recombinant protein at 1.5 mg/ml is possible because transgenic mammals can express recombinant proteins at a wide range of concentration values. The number of mammals that need to be generated may be large in order to obtain one, and while generating a large number of mammals is laborious, it is not undue. As indicated above, the method steps taught by Meade et al. and Velander et al. are the same as those disclosed in the instant specification. While the claims require the recombinant protein be expressed at a certain level, an artisan practicing the same methods steps as disclosed by Meade et al., Velander et al., and the instant specification would predictably arrive at mammals expressing recombinant proteins in milk at 1.5 mg/ml.

Applicant indicates that the references do not include all Applicant's claimed elements. Applicant indicates that Meade et al. do not include prothrombin in milk derived from a transgenic mammal (Applicant's response, page 5-6). In response, this is not persuasive. Meade et al. is not cited as a 102 rejection. Meade et al. is cited as a 103 in combination with other references. With regard to the teaching of human prothrombin, the Examiner relied on Jorgensen et al. who teach the cDNA sequence encoding human prothrobmin. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant indicates that Meade et al. uses the term "large quantities" only once in an attempt to frame a goal that has advantages over cell culture secretion. However, Meade et al. teach 0.2-0.5 ug/ml of TPA in milk, which is one-thousand times lower than the Applicant's claimed embodiment (Applicant's emphasis, Applicant's response, page 6). In response, this is not persuasive. As discussed above, Velander et al. teach that recombinant protein can be expressed at 1 mg/ml. Further, as illustrated by Velander et al. and Meade et al., transgenic mammals express recombinant proteins in milk at a range of concentrations. Thus, given these teachings, an artisan would have predicted with reasonable expectation of success that one could obtain proteins expressed at the claimed 1.5 mg/ml. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually

where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant indicates that Jorgensen et al. do not include prothrombin in milk derived from a transgenic mammal (Applicant's response, page 6). In response, Jorgensen et al. was not cited in a 102 rejection, but in a 103 rejection. The Examiner relied on Meade et al. and Velander et al. for teaching that recombinant proteins can be secreted into milk. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant indicates that Seegers et al. does not include the Applicant's claimed prothrombin expression concentration. Seegers provides no teaching of a milk composistion derived from a transgenic mammal comprising human prothrombin protein or amino acid sequence (Applicant's response, page 7). In response, this is not persuasive. Seegers et al. was not cited in a 102 rejection, but in a 103 rejection. Seegers et al. was cited to show that prothrombin can be treated with sodium citrate, wherein sodium citrate processes prothrombin into thrombin (Seegers et al., page 42, 3rd parag.). This addresses the limitation of claim 57. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of

references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant indicates that van Cott et al. does not include prothrombin in milk derived from a transgenic mammal (Applicant's response, page 7). In response, this is not persuasive. van Cott et al. was not cited in a 102 rejection, but a 103 rejection. van Cott et al. was cited to show that when recombinant proteins are secreted in milk, they are processed with appropriate protein modifications such as gamma-carboxylation (van Cott and Velander, page 1686, 2nd col., 3rd parag.). As such, given the combination of Meade et al., Jorgensen et al., van Cott and Velander et al., and Velander et al., 1992, an artisan would have reasonable expectation of success in obtaining a transgenic mammal that expresses human prothrombin, wherein the prothrombin is gamma-carboxylated. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant indicates that Velander does not include the Applicant's claimed prothrombin expression concentration. Applicant indicates that Velander et al. does not disclose a milk composition comprising prothrombin (Applicant's response, page 8). In response, this is not persuasive. Velander et al. was not cited in a 102 rejection, but in a 103 rejection. Velander et al. was cited to show that transgenic mammals can produce mg/ml of a protein of interest in milk (Velander et al., page 12005, 1st col.,

parag. under “Protein Analysis," see also Figure 1). Given this teaching, an artisan would have expected that in combination with the teachings of Meade et al., Jorgensen et al., an artisan would have reasonable expectation of success in obtaining a transgenic mammal that expresses human prothrombin. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant indicates that claims 40, 42, 56, 58 are not obvious under Meade et al., Jorgensen et al., Le Bonniec et al., and Velander et al. Applicant indicates that this rejection is responded to by incorporating by reference the arguments presented regarding Meade et al., Jorgensen et al., and Velander et al., as discussed above. The Examiner has not found that Le Bonneic et al. discloses a milk composition derived from a transgenic mammal containing a human protein amino acid sequence at a concentration of at least 1.5 mg/ml (Applicant’s response, pages 8-9). In response, this is not persuasive. Le Bonneic et al. was not cited in a 102 rejection, but in a 103 rejection. Le Bonneic et al. was cited to address claim 58, wherein prothrombin can be activated by bovine factor Xa, in the presence of bovine factor Va, phospholipids, and calcium (Le Bonnic et al., page 13799, 1st col., 2nd parag.). Given the combination of teachings of Meade et al., Jorgensen et al., Velander et al., and Le Bonneic et al., an artisan would have would have reasonable expectation of success in obtaining a transgenic mammal that expresses human prothrombin, wherein the prothrombin is

activated by bovine factor Xa, in the presence of bovine factor Va, phospholipids, and calcium. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regard to the rejection of claims 40 and 57 as not being obvious over Meade et al., Jorgensen et al., Seegers et al., Le Bonniec et al., and Velander et al., Applicant indicates that the rejection is responded to by incorporating by reference the arguments presented regarding Meade et al., Jorgensen et al., Seegers et al., and Velander et al., as discussed above. The Examiner has not found that Le Bonniec et al. disclose a milk composition derived from a transgenic mammal containing human prothrombin at a concentration of at least 1.5 mg/ml (Applicant's response, page 9). In response, as discussed above, Le Bonneic et al. was not cited in a 102 rejection, but in a 103 rejection. Le Bonneic et al. was cited to address claim 58, wherein prothrombin can be activated by bovine factor Xa, in the presence of bovine factor Va, phospholipids, and calcium (Le Bonnic et al., page 13799, 1st col., 2nd parag.). Given the combination of teachings of Meade et al., Jorgensen et al., Velander et al., and Le Bonneic et al., an artisan would have would have reasonable expectation of success in obtaining a transgenic mammal that expresses human prothrombin, wherein the prothrombin is activated by bovine factor Xa, in the presence of bovine factor Va, phospholipids, and calcium. In response to Applicant's arguments against the references individually, one

cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Thus, the claims remain rejected.

Conclusion

No claims allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Wednesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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/Joanne Hama/
Primary Examiner
Art Unit 1632